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Molar incisor hypomineralization: a study of aetiological factors in a group of UK children*

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Objectives. The objectives were to investigate the aetiology of molar incisor hypomineralization (MIH), and to discuss previously published studies. **Subjects and methods.** One hundred and nine children attending the Department of Paediatric Dentistry at the Royal London Hospital were included in the study: 57 children with MIH and 52 controls. Their mothers completed a medical history interview. **Results.** No significant associations were found with MIH and delivery and birth complications, breastfeeding, immunization history, other illnesses and allergies, general anaesthetics, fluoride history, and trauma or abscesses affecting the primary predecessors. A family history of enamel defects was more commonly reported for MIH children, but the association was not statistically significant. However, MIH was significantly more common among those whose mothers had experienced problems during pregnancy ($P = 0.025$), those who had chickenpox between the ages of 3 and 3.99 ($P = 0.047$), and those for whom amoxycillin was the only antibiotic they had received ($P = 0.028$). **Conclusions.** The aetiology of MIH remains unclear, and this study questions whether it is because of a lone aetiological insult. This study recommends further research looking at the links with chickenpox occurring around the third year of life and amoxycillin.

Introduction

Molar incisor hypomineralization (MIH) was first noted in Sweden in the late 1970s[1]. In view of the chronological distribution of enamel defects, Weerheijm *et al*. in 2001 defined MIH as hypomineralization of systemic origin of one to four first permanent molars frequently associated with affected incisors[2]. The exact nature of the systemic insult is poorly defined, although an increase in childhood illness has been implicated.

It is known that enamel formation begins about week 20 *in utero* for the crowns of the permanent first molars, 3–4 months for the central incisors and lower laterals and 10–12 months for the upper lateral incisors. It is thought to take about 3 years for crown formation to complete. Therefore, research into the aetiology of MIH has concentrated on an environmental insult occurring in the first 3 years of life because of the pattern of molars and incisors affected.

Ameloblasts are extremely sensitive, and if disturbed during their secretory phase, you get a reduced thickness of normal enamel which is hypoplasia. However, as it is opacities that occur in MIH, the ameloblasts must be affected in the later mineralization or maturation phase of amelogenesis[3,4].

The aim of this study was to investigate the aetiology of MIH in children attending the Department of Paediatric Dentistry at the Royal London Hospital.

Subjects and methods

The research protocol was submitted to the appropriate ethics committee, and consent was obtained for each child selected for the study. The children were all attending the Department of Paediatric Dentistry at The Royal London Hospital. Eight pilot medical history

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interviews were conducted and revisions were made. At the pilot stage, fathers were found to have poor recall when questioned about the pregnancy. Therefore, for both the case and control groups, the children had to be attending with their mothers. Children attending with their fathers, other family members, adoptive parents, or other legal guardians were excluded to ensure that the questions about the pregnancy were answered as factually as possible.

Patient sample

All children presenting with MIH during a 1-year period were invited to participate in the study. The majority of these were referrals from general practice, but children under routine care on the department were also included. The controls were patients attending the department during the same period for routine care, not manifesting hypomineralization and matched for similar age, sex, socioeconomic grouping, and ethnic grouping. There were no non-participants for either group.

There were 109 children in the study, 57 in the MIH case group and 52 in the control group. The mean age was 8.7 years (range 6.0–13.0 years) with 46 boys and 63 girls. Demographic details are shown in Table 1.

Exclusion criteria for the study group included patients with generalized enamel defects caused by amelogenesis imperfecta or with enamel hypoplasia suggesting a specific chronological event. Controls were excluded if the molars were not fully erupted. Children with grossly carious first permanent molars or traumatized incisors with tissue loss were not included.

The medical history interview

A detailed medical history interview was conducted with the mothers of the case and control group children. There were over 60 questions relating to the child's medical history up to the age of 4. These were divided into sections on pregnancy, delivery details, birth weight and prematurity, breastfeeding, immunizations, illnesses, allergies, operations, antibiotic usage, fluoride usage, history of trauma or infection to the primary teeth, and family history of enamel defects. The child health record provided by the mother was referred to where necessary, and mothers had the opportunity to submit subsequent information if they could not recall specific information at the time of the interview. The interview took on an average 20–25 min to complete, and all interviews were conducted by one examiner (R.W.) face-to-face with the mother. The questions were asked in the same order using a set banter to avoid bias, and responses were recorded by the examiner using a clinical proforma.

Analysis of data

Data were coded and entered onto a database (SPSS 11.5.0 for Windows; SPSS Inc., Chicago, IL, USA) prior to carrying out a descriptive analysis. Chi-squared statistics, Mann–Whitney *U*-test statistics, and independent sample *t*-tests were used for testing differences between groups. Relative risk was estimated using odds ratios with 95% test-based confidence intervals.

Results

Analysis of the 109 interviews revealed that MIH was significantly more common among

Table 1. Demographic details of the molar incisor hypomineralization (MIH) group compared to the control group – gender and age.

	MIH group		Control group				
Variable	***n***	**%**	***n***	**%**	**Odds ratio**	**95% Confidence interval**	***P***
Male	25	43.9	21	40.4	1.15	0.54–2.47	0.714
Female	32	56.1	31	59.6	0.87	0.4–1.86	0.714
Total	57	100.0	52	100.0			
Variable	Mean	SD	Mean	SD	ΣMean	ΣSD	*P*
Age (year)	8.51	1.33	8.85	2.00	8.67	1.68	0.298*

*Independent sample *t*-test.
SD, standard deviation.

Table 2. The distribution of pregnancy and birth variables among children within the molar incisor hypomineralization (MIH) and the control groups (summary).

Variable	MIH *n* = 57 Yes	Control *n* = 52 Yes	Odds ratio	95% Confidence interval	*P*
Problems with pregnancy	21 (36.8%)	9 (17.3%)	2.787	1.14–6.84	0.025
Gestational diabetes	3	1	2.83	0.29–28.13	0.374
Rhesus disease	1	0	–	–	1.000
Hypertension	5	1	4.90	0.55–43.45	0.153
Pre-eclampsia	0	0	–	–	–
Other	12	7	1.71	0.62–4.75	0.300
Number of ultrasound scans	Mean 3.54	Mean 2.76			0.200*
	SD 3.84	SD 1.93			
Prematurity	7	5	1.32	0.39–4.43	0.658
Delivery type: normal	38	40	0.60	0.26–1.4	0.238
Birth complications	20	12	1.80	0.77–4.19	0.171
Birth weight: LBW (< 2.5 kg)	9	3	2.88	0.73–11.29	0.130

*Independent sample *t*-test.
LBW, low birth weight; SD, standard deviation.

Table 3. The distribution of illnesses among children within the molar incisor hypomineralization (MIH) and the control groups throughout their lives (summary).

Variable	MIH *n* = 57 Yes	Control *n* = 52 Yes	Odds ratio	95% Confidence interval	*P*
Had chickenpox	51	43	2.67	0.77–9.27	0.123
Age had chickenpox: < 1 year	3	2	1.29	0.2–8.15	0.786
Age had chickenpox: 1–1.99 year	2	4	0.40	0.07–2.3	0.303
Age had chickenpox: 2–2.99 years	7	4	1.57	0.42–5.82	0.500
Age had chickenpox: 3–3.99 years	16 (28.1%)	6 (11.5%)	2.93	1.02–8.47	0.047
Age had chickenpox: > 4 years	18	23	0.45	0.19–1.07	0.070
Diarrhoea and vomiting	11	9	1.14	0.43–3.03	0.789
Chest infections	14	16	0.73	0.32–1.7	0.469
Ear infections	15	15	0.88	0.38–2.04	0.768
Urinary tract infections	7	10	0.59	0.21–1.68	0.321
Unexplained high fever	8	14	0.44	0.17–1.16	0.099
Cardiac problems	3	5	0.52	0.12–2.3	0.391
Kidney problems	2	3	0.59	0.1–3.7	0.577
Asthma	14	12	1.09	0.45–2.62	0.856
Diabetes	0	0	–	–	–
Epilepsy	0	1	–	–	1.000
Eczema	6 (10.5%)	15(28.8%)	0.29	0.1–0.82	0.019
Other illness	14	7	2.09	0.77–5.68	0.147
Allergies	12	13	0.80	0.33–1.96	0.625

the following: those whose mothers had experienced problems during pregnancy ($P = 0.025$; Table 2), those who had chickenpox between the ages of 3 and 3.99 ($P = 0.047$; Table 3), and those for whom amoxycillin was the only antibiotic they had ever received ($P = 0.028$; Table 4).

No associations were found with MIH and delivery and birth complications (Table 2); breastfeeding variables; immunization history including measles, mumps, and rubella; other illnesses and allergies (Table 3); general anaesthetics (Table 4); fluoride history (Table 5); and trauma or abscesses affecting the primary predecessors (Table 6). A family history of enamel defects was more commonly reported for children with MIH (Table 6), but the association was not statistically significant.

Children in the control group had more eczema ($P = 0.019$; Table 3), mixed antibiotic use ($P = 0.040$; Table 4), and had experienced more abscesses affecting the primary predecessors ($P = 0.004$; Table 6).

Table 4. The distribution of medications and interventions among children within the molar incisor hypomineralization (MIH) and the control groups (summary).

Variable	MIH *n* = 57 Yes	Control *n* = 52 Yes	Odds ratio	95% Confidence interval	*P*
Number of GAs	Mean 0.49	Mean 0.90			0.849*
	SD 0.78	SD 2.38			
Antibiotic use	49	46	0.61	0.17–2.22	0.452
Antibiotic type: mixed antibiotic use	6 (10.5%)	13 (25.0%)	0.33	0.11–0.95	0.040
Antibiotic type: penicillin only	2	2	0.88	0.12–6.49	0.896
Antibiotic type: amoxycillin only	33 (57.9%)	19 (36.5%)	2.55	1.11–5.89	0.028
Antibiotic type: erythromycin only	1	1	0.88	0.05–14.46	0.927
Antibiotic type: trimethoprim only	1	0	–	–	1.000
Age had first antibiotics: at birth	4	5	0.72	0.18–2.89	0.648
Age had first antibiotics: < 1 year	17	13	1.35	0.56–3.28	0.503
Age had first antibiotics: 1–1.99 year	8	4	2.05	0.57–7.39	0.271
Age had first antibiotics: 2–2.99 years	10	7	1.43	0.49–4.17	0.514
Age had first antibiotics: 3–3.99 years	2	4	0.44	0.08–2.55	0.362
Age had first antibiotics: > 4 years	5	10	0.40	0.13–1.29	0.126
Number of antibiotic courses	Mean 6.02	Mean 5.58			0.221*
	SD 4.82	SD 5.45			

*Mann–Whitney *U*-test.
GA, general anaesthesia; SD, standard deviation.

Table 5. The fluoride history among children within the molar incisor hypomineralization (MIH) and the control groups.

Variable	MIH *n* = 57 Yes	Control *n* = 52 Yes	Odds ratio	95% Confidence interval	*P*
Age started brushing with toothpaste: < 6 months	4	7	0.50	0.14–1.83	0.298
Age started brushing with toothpaste: 6–11 months	25	17	1.72	0.78–3.8	0.177
Age started brushing with toothpaste: 12–17 months	13	7	1.99	0.72–5.49	0.182
Age started brushing with toothpaste: 18–23 months	3	4	0.69	0.15–3.25	0.640
Age started brushing with toothpaste: > 24 months	9	16	0.44	0.17–1.11	0.081
Toothpaste type: children's	53	46	1.73	0.46–6.5	0.418
Toothpaste type: adult	4	6	0.58	0.15–2.18	0.418
Swallowed toothpaste	23	23	0.93	0.43–2.02	0.861
Fluoride supplements under 4 years	6	8	0.65	0.21–2.01	0.449

Table 6. Distribution of general variables among children within the molar incisor hypomineralization (MIH) and the control groups.

Variable	MIH *n* = 57 Yes	Control *n* = 52 Yes	Odds ratio	95% Confidence interval	*P*
Average days off school per typical term	Mean 2.32	Mean 2.17			0.098*
	SD 9.26	SD 2.90			
Trauma to primary incisors	9	13	0.56	0.22–1.45	0.235
Abscess affecting primary incisors	6 (10.5%)	18 (34.6%)	0.22	0.08–0.62	0.004
Family history of enamel defects	22	14	1.71	0.76–3.84	0.197

*Mann–Whitney *U*-test.
SD, standard deviation.

Discussion

In this study, MIH was significantly more common among those whose mothers had experienced problems during pregnancy ($P = 0.025$). Only one previous study found a link with urinary tract infection in the later stages of pregnancy[5]. In this study, however, when the results were split down into the possible problems occurring in pregnancy, for example, gestational

diabetes, no significant differences were found between the cases and the controls.

No associations were found between MIH and the number of ultrasound scans during the pregnancy, prematurity, delivery requiring induction, mode of delivery, delivery and birth complications, birth weight category, and neonatal jaundice. This is in agreement with a previous study[6]. However, one study found 48% of MIH children had a medical problem related to birth, e.g. premature birth, excessively prolonged duration of delivery, or cyanosis[7].

Prolonged breastfeeding and exposure to the environmental contaminant dioxin have been linked to MIH-type defects in Finland[8–10]. As for previous studies, however, this study did not find any difference between the groups with regard to whether the child was breastfed, duration of breastfeeding, and problems with milk[6,11,12].

No association was found between whether or not the child had suffered from chickenpox or its severity. Interestingly, when the data were split into the ages they had chickenpox, those experiencing it between the ages of 3 and 3.99 had a statistically significant association with MIH ($P = 0.047$). This is the first study to show this. It could be that the ameloblasts are more susceptible at this age when they are in the transitional stages of enamel maturation[13].

Chickenpox is caused by the varicella zoster virus which is a member of the herpes family of viruses. It tends to affect young children and is thought to be transmitted by inhalation. It replicates in the mucosa of the respiratory tract, then is disseminated via the lymphatics and the bloodstream before arriving at its main target organ – the skin. This results in crops of vesicles which progress to become pustules then scabs caused by degenerative changes in the epithelial cells.

It is known that the virus spreads to many other epithelial surfaces including the lung. However, infections at these sites do not normally manifest clinically presumably as little or no damage results. It is possible that the epithelial-derived ameloblasts at the maturation phase are also affected. Because enamel is not capable of remodelling, scarring may occur presenting clinically as opacities. The patchy distribution of chickenpox skin lesions could be akin to the asymmetric distribution of MIH defects.

There are at least four different strains of varicella zoster virus. Strains B and C occur in cooler climates, whereas others are specific to tropical countries[14]. Certain strains affect adults rather than children. If the virus was found to be implicated in the aetiology of MIH, the differences in the strains could therefore account for reported geographical differences in the prevalence of MIH.

Unlike in earlier studies, no difference was found with regard to ear infections, respiratory infections and asthma, and unexplained high fevers[6,7,12]. This was in agreement with a study which found no differences in reported illnesses in the first 2 years of life between study and control groups[9].

When looking at the children's exposure to antibiotics, no differences were found between the groups with regard to whether or not they had ever had antibiotics, the age they had first had them, and the mean number of courses. When antibiotic usage was split into types, there were no significant differences between those who had received only erythromycin, penicillin, trimethoprim, or any 'other' unspecified antibiotic. The control group, however, had been given significantly more mixed antibiotics ($P = 0.040$), and the case group was more likely to have had amoxycillin only ($P = 0.028$). This does not provide firm evidence that amoxycillin is an aetiological agent in MIH as amoxycillin would have been included in the mixed antibiotic group which was more common in the controls. Had both 'amoxycillin only' usage and 'mixed antibiotic' usage occurred statistically significantly more in the MIH group, amoxycillin may have been of concern. Amoxycillin was the most commonly given antibiotic in both the case and control groups reflecting current prescribing trends.

Children prescribed with antibiotics are usually ill, and it is not possible to determine whether the medicine or the disease is the cause of the enamel defect. Tetracycline is the only antibiotic known to cause developmental defects of teeth.

A family history of enamel defects was more commonly reported for children with MIH, but the association was not statistically significant. This was in line with the findings of Jälevik *et al.*[12] Mothers, however, found it difficult

to differentiate between 'bad teeth' and enamel developmental defects.

Discussion of aetiological theories

Because only the first permanent molars and incisors are affected in MIH, much focus has been given to an environmental insult in the enamel-formative years for these teeth. However, the permanent canines also start to form at 3–4 months of age so theoretically should also be affected if MIH is caused by an environmental insult, but are often not erupted at the time of examination. During this study, several children were seen to have opacities on their canines. They were excluded from participation in the project as a diagnosis of a hypomaturation form of amelogenesis imperfecta could not be ruled out. There have been reports of increased wear of the permanent canine tips.

In MIH, the enamel defects on the molars and incisors can occur asymmetrically whereas in a chronological hypoplasia (having an identified acquired insult), defects are usually symmetrical. Again, this questions whether there is environmental cause for MIH and may point to a genetic factor. However, asymmetry could be explained by different groups of ameloblasts being active or switched on at the time of the environmental insult, and it is known that the body as a whole develops asymmetrically.

Problems in diagnosing causes of enamel defects

Non-specific appearance of enamel defects

Although many aetiological agents are known to be responsible for enamel defect, it is rarely possible to identify the particular aetiological factor that causes it[15]. For example, Suckling and Pearce[16], in an aetiological study of developmental defects in New Zealand children, were unable to establish the aetiological factors responsible for the majority of defects. They found that common childhood illnesses during the period of tooth formation did not alter the prevalence of defects, but these did increase significantly in children with a history of a serious illness. A later study by Suckling *et al.*[17] also demonstrated the difficulties in establishing the aetiology of the majority of enamel defects. The main reason for this is that ameloblasts can only respond to any number of insults in two ways – hypoplasia or opacities. For example, teeth affected by the hypomaturation form of amelogenesis imperfecta resemble fluorosis.

Threshold levels

The threshold levels for aetiological agents to cause enamel defects are not known, particularly as ameloblasts are more or less sensitive at the different stages of formation. The complexity of the relationship between degree of injury and effect on ameloblasts has been shown in animal experiments revealing that acute and chronic systemic disorders produce different responses in ameloblast function[18]. In acute systemic disorders, the ameloblasts are more susceptible to injury at the stage of matrix formation, which presents clinically as hypoplasia.

Likewise, there may be subclinical chronic conditions that may be of sufficient intensity to cause enamel opacities, without producing any systemic clinical symptoms in the child[19]. For example, in MIH, a subclinical viral infection could result in opacities, but this would not explain why only certain teeth are affected.

Insult synergy

Systemic conditions probably act synergistically to produce enamel defects. Single causative factors at low thresholds may not have an effect, but the simultaneous occurrence of two or more insults may result in enamel defects[19].

Difficulties in timing of events

Identifying possible aetiological agents involves linking the estimated time of formation of the enamel defect with the time the insult occurred. This is easier for hypoplastic defects than opacities. For opacities, the timing of events relative to the position of the defect is often not conclusive because data on the chronology of development and mineralization of

human enamel are limited, and derived from relatively few samples[4]. Also, the range of normal values for enamel formation is wide, so a particular insult cannot be identified as the causative agent unless no other possible insult has occurred during that time. This is unlikely in children, particularly between the ages of 6 months to 2 years when several common childhood illnesses commonly occur. Further work on the time frame of amelogenesis and particularly the maturation phase is required.

Limitations

It should be remembered that this was a retrospective study and relied on the memories of the mothers interviewed. Despite the extensive questioning, the obtained data will not be a complete reflection of the child's medical history over the first 4 years of life. A previous study tried to minimize parental omissions by obtaining children's medical notes, but only 60% of doctors were willing to cooperate and often the reports were too briefly worded to be of use[7]. This illustrates that prospective studies are required.

Retrospective information may be biased by knowledge about the diagnosis, that is, there is a risk of recall bias. However, recall bias is unlikely in this study as the parents were not informed of possible aetiological theories before answering the questionnaire.

It should be remembered that in any study with a large number of questions, at least one variable may appear to be significant by chance.

The case and control children in this study were of similar ages and socioeconomic groupings because environmental conditions have been mentioned in the literature as a possible cause of MIH[1]. Therefore, because of this correction, it is not possible to say anything about their influence on the development of MIH.

Conclusions

As with previous studies, this paper fails to show one specific aetiological factor associated with MIH. MIH may well have a multifactorial aetiology with the possibility of a genetic susceptibility, and family studies may provide further information. For example, MIH could be an autosomal recessive condition or a previously unrecognized form of localized amelogenesis imperfecta, like that diagnosed by Winter[20].

As illustrated with chickenpox, the timing of the insult may be more significant than the insult itself, and this study would suggest age 3–4 years as a critical time. Countries routinely vaccinating against varicella zoster virus, such as America[21], should be observed to determine any decline in the prevalence of MIH.

A further understanding of the aetiology and timing may help us to identify at-risk children.

What this paper adds

- This paper reviews the literature on aetiological theories of MIH.
- It draws attention to the problems associated with finding the causes of enamel defects.
- It proposes that the timing of the aetiological insult, for example, chickenpox infection or the prescription of amoxycillin, could be more important than the insult itself.

Why this paper is important to paediatric dentists

- It highlights that the cause of MIH is still not known and caution is advised when discussing this with parents.
- This paper indicates the need for high-quality prospective studies in this area, and genetic studies.

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